REMARKS

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Claims 1-10 were pending in this application when examined.

Claim 1 is amended to recite "a light-stabilizing effective amount of 0.2 w/v% or more". Support for this amendment can be found on page 5, lines 17-21 of the specification.

Claim 2 is amended to correspond with the amendment to claim 1.

Support for new claim 12 can be found on page 5, lines 10-15 of the specification.

Support for new claim 13 can be found on page 2, lines 26-33 and page 4, lines 2-5 of the specification.

I. Declaration

The Declaration filed on January 5, 2009 has been considered, but the Examiner states that the evidence submitted in support of unexpected results is not found persuasive, because the exemplified preparations are not commensurate in scope with the claims. Claim 1 is amended to recite "a light-stabilizing effective amount of 0.2 w/v% or more". Thus, claim 1 now includes a specific light-stabilizing effective amount.

Accordingly, the showing of unexpected results is commensurate in scope with the claims.

II. Claim Rejection Under 35 U.S.C. § 112

The Examiner rejects claims 1-10 under 35 U.S.C. § 112, first paragraph, because the specification, **while enabling for** an aqueous liquid preparation comprising, in an aqueous solution, (S)-4-[4-[(4-chlorophenyl)-(2-pyridyl)-methoxy]-piperidino]-butanoic acid or a pharmaceutically acceptable acid addition salt thereof, and a low molecular weight water-soluble metal chloride in a light-stabilizing effective amount of **0.2% or more**, does not reasonably provide enablement for preparations comprising any water-soluble metal chloride in a light-stabilizing effective amount of less than 0.2%, or any high molecular weight water-soluble metal chlorides.

Claim 1 is amended to recite "a water-soluble metal chloride in a light-stabilizing effective amount of **0.2 w/v% or more**", and, as acknowledged by the Examiner, the specification is enabling for "0.2 w/v% or more".

Moreover, Experimental Example 1 in the present specification shows that Formulation 2, containing 0.1% of sodium chloride, forms a precipitate, and Formulation 3, containing 0.2% of sodium chloride, is stable with no change from the time of preparation (see page 7, line 21 – page 8, line 15). Thus, one of ordinary skill in the art would be capable of making and using the claimed aqueous liquid preparation without undue experimentation.

Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

III. Claim Rejection Under 35 U.S.C. § 103

The Examiner rejects claims 1-10 under 35 U.S.C. § 103(a) as being unpatentable over Kita et al. (U.S. 6,307,052) ("Kita") and Stevenson et al. (U.S. 4,053,628) ("Stevenson"). As applied to the amended claims, Applicant respectfully traverses the rejection.

One of ordinary skill in the art would not have been motivated to combine the teachings of the references, as suggested by the Examiner.

Kita discloses benzenesulfonate (bepotastine), and discloses a benzoate of an optically-active piperidine derivative, (+)-(S)-4-[4-[(4-chlorophenyl)(2-pyridyl)methoxy]piperidino] butylic acid.

Stevenson discloses, for example, that Antazoline and diphenhydramine can be optionally added as anti-histamine compounds (see col. 3, lines 14-16). Bepotastine, which is used in the present application, is a **piperidine derivative** (see Kita, Abstract, and enclosed Merck Index, item 1149). However, the two anti-histamine compounds disclosed in Stevenson (Antazoline and diphenhydramine) do not have a piperidine skeleton (see Merck Index, item 680 and item 3309).

Those having ordinary skill in the art consider compounds with different chemical structures to have different physical properties, even when the compounds have the same pharmacological effects. Accordingly, one of ordinary skill in the art would consider bepotastine to have different physical properties from those of Antazoline and diphenhydramine, because bepotastine is a piperidine derivative and Antazoline and diphenhydramine are not piperidine derivatives.

Moreover, the goal of the present invention is to solve the light instability problem associated with bepotastine, such as coloring and precipitation (see specification, page 1, line 30 – page 2, line 2). Stevenson does not describe a problem related to the light-stabilization of anti-histamine compounds, and the reference does not teach or suggest that metal chlorides contribute to light-stabilization.

In addition, Stevenson describes that 0.25-5% of an additive can be used, such as glycerin (see col. 3, lines 59-67, and col. 4, lines 1-2). **However, in Experimental Examples 1-4 of the present application, Formulations 8, 9 and 13-17 showed no light-stabilizing effect of bepotastine by the addition of 0.5-2.2% of glycerin. A light-stabilizing effect of bepotastine was observed only with water-soluble metal chloride.**

Furthermore, the Examiner has combined the references based upon impermissible hindsight analysis. Stevenson discloses an eye-drop solution containing cromoglycate and sodium chloride in Examples 1 and 3. However, the reference merely discloses one of the three types of water-soluble metal chlorides for which the light-stabilizing effect of bepotastine was clearly observed in the Experimental Examples of the present application.

The reference does not teach or suggest that water-soluble metal chlorides can be used in a light-stabilizing effective amount with a preparation comprising bepotastine. It would not have been obvious to one of ordinary skill in the art that only a water-soluble metal chloride, among many additives disclosed in Stevenson, has a light-stabilizing effect on bepotastine, absent Applicant's claims.

Accordingly, the Examiner has combined the references solely using Applicant's claims as a roadmap, which is clearly improper.

In view of the foregoing, claim 1 would not have been obvious over Kita in view of Stevenson.

Claims 2-10 depend directly or indirectly from claim 1, and thus also would not have been obvious over the references.

IV. New Claims

Claim 12 depends from claim 1, and is thus distinguished over the references for the reasons discussed above with respect to claim 1.

Claim 13 is directed to an aqueous eye drop comprising (+)-(S)-4-[4-[(4-chlorophenyl)(2-pyridyl)methoxy]piperidino]butyric acid or a pharmacologically acceptable acid addition salt thereof, which is light-stabilized with a water-soluble metal chloride at not less than 0.2 w/v%. It is distinguished over the cited references, because one of ordinary skill in the art would not have been motivated to combine the references to arrive at the aqueous eye drop of claim 13 for the reasons discussed above with respect to claim 1.

Accordingly, prompt examination and allowance of claims 12-13 are respectfully requested.

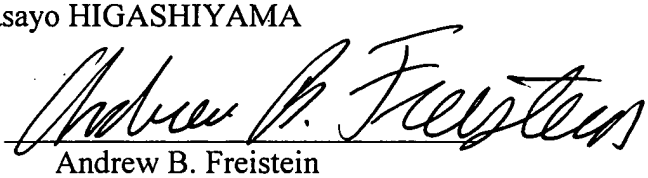
V. Conclusion

For these reasons, Applicant takes the position that the presently claimed invention is clearly patentable over the applied references.

Therefore, in view of the foregoing amendments and remarks, it is submitted that the rejections set forth by the Examiner have been overcome, and that the application is in condition for allowance. Such allowance is solicited.

Respectfully submitted,

Masayo HIGASHIYAMA

By 

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Enclosure: The Merck Index, pages 110-111, 188-189 and 560-561 (2006)

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1137. Benzylideneacetone. [122-57-6] 4-Phenyl-3-buten-2-one; benzalacetone; methyl styryl ketone; cinnamyl methyl ketone; acetocinnamone. $C_{10}H_{10}O$; mol wt 146.19. C 82.16%, H 6.89%, O 10.94%. $C_6H_5CH{=}CHCOCH_3$. Prepd by condensing acetone and benzaldehyde by means of aq alkali: Drake, Allen, *Org. Synth.* 3, 17 (1923).

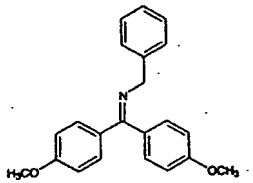
Lustrous plates on vacuum distillation. Coumarin type odor. Purification by steam distillation: Fromm, Haas, *Ann.* 394, 291 (1912). mp 41.5°. d_{15}^{15} 1.0377; $d_4^{45.2}$ 1.0097. bp_{760} 261°; bp_{250} 211°; bp_{100} 187.8°; bp_{50} 161.3°; bp_{20} 143.8°; bp_{10} 127.4°; bp_5 112.2°; $bp_{1.6}$ 81.7°. $n_D^{45.9}$ 1.5836. Absorption spectrum: Baker, *J. Chem. Soc.* 91, 1492 (1907); Baly, Schäfer, *ibid.* 93, 1813 (1908). Freely sol in alcohol, benzene, chloroform, ether; sparingly sol in water, petr ether.

USE: In perfumery, organic syntheses.

1138. Benzylideneaniline. [538-51-2] *N*-(Phenylmethylene)benzenamine; benzalaniline. $C_{13}H_{11}N$; mol wt 181.23. C 86.16%, H 6.12%, N 7.73%. $C_6H_5N{=}CHC_6H_5$. Prepd by the action of aniline on benzaldehyde: Bigelow, Eatough, *Org. Synth.* coll. vol. I (2nd ed., 1941) p 80. Molecular structure: M. Traetteberg *et al.*, *J. Mol. Struct.* 48, 395 (1978).

Plates from 85% alc. Has been obtained as the yellow modification (needles from CS_2). The colorless form melts at 48°, after solidifying melts again at 56°. d_4^{20} 1.045. bp_{760} 300°. Absorption spectrum: Baly *et al.*, *J. Chem. Soc.* 97, 590 (1910). Sol in alcohol, chloroform, acetic anhydride, carbon disulfide.

1139. Benzylimidobis(*p*-methoxyphenyl)methane. [524-96-9] *N*-[Bis(4-methoxyphenyl)methylene]benzenemethanamine. $C_{29}H_{27}NO_2$; mol wt 331.41. C 79.73%, H 6.39%, N 4.23%, O 9.66%. Prepd by heating *p,p'*-dimethoxybenzophenone, thionyl chloride and benzylamine: Schönberg, Urban, *Ber.* 67, 1999 (1934).



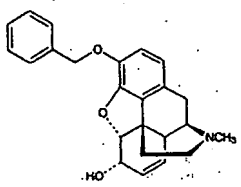
Pale-yellow crystals, mp 89-91°. Soluble in ether, chloroform. Slightly sol in petr ether.

USE: Detection of elementary sulfur.

1140. Benzyl Methyl Ether. [538-86-3] (Methoxymethyl)benzene; methyl benzyl ether. $C_8H_{10}O$; mol wt 122.16. C 78.66%, H 8.25%, O 13.10%. $C_6H_5CH_2OCH_3$. Prepd from benzyl chloride, methanol, and NaOH: Olson *et al.*, *J. Am. Chem. Soc.* 69, 2451 (1947).

Liquid. d 0.987. bp 174°. Practically insol in water. Sol in alcohol, ether.

1141. Benzylmorphine. [14297-87-1] 7,8-Didehydro-4,5-epoxy-17-methyl-3-(phenylmethoxy)morphinan-6-ol. $C_{24}H_{25}NO_3$; mol wt 375.46. C 76.77%, H 6.71%, N 3.73%, O 12.78%. Prepn from morphine and benzyl chloride in the presence of sodium ethylate: DE 91813 (1897 to E. Merck), *Frdl.* 4, 1245; from morphine and benzyldimethylphenylammonium hydroxide: Rodionow, *Bull. Soc. Chim. Fr.* [4] 45, 109 (1929). Properties of hydrochloride: Dott, *Pharm. J.* 115, 757 (1925).



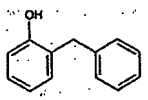
Needles from water, prisms or platelets from ether, chloroform, mp 132°. Soluble in 2500 parts cold water, more sol in boiling water; 1.6 parts dissolves in 100 parts ether; readily sol in 50% alcohol, benzene.

Hydrochloride. Peronine. $C_{24}H_{25}NO_3{\cdot}HCl$. Monohydrate, needles from water. Sol at 15° in 133 parts water, 218 parts 95% alcohol, 390 parts chloroform, 400 parts methanol; slightly sol in abs alcohol; very slightly sol in ether, acetone, isoamyl alcohol.

Note: This is a controlled substance (opium derivative): 21 CFR, 1308.11.

THERAP CAT: Analgesic (narcotic).

1142. *o*-Benzylphenol. [28994-41-4] 2-(Phenylmethyl)-phenol; *o*-phenyl-*o*-cresol; (2-hydroxydiphenyl)methane. $C_{13}H_{12}O$; mol wt 184.23. C 84.75%, H 6.57%, O 8.68%. Prepn from benzyl bromide and sodium phenoxide: Kornblum, Lurie, *J. Am. Chem. Soc.* 81, 2711 (1959).



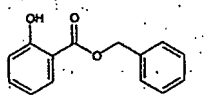
Crystals or liquid. mp 20.2-20.9°. bp_{10} 154-156°; $bp_{1.0}$ 121-123°. n_D^{20} 1.59945. Practically insol in water. Sol in organic solvents, in fixed alkali hydroxide solns.

1143. *p*-Benzylphenol. [101-53-1] 4-(Phenylmethyl)phenol; *o*-phenyl-*p*-cresol; (4-hydroxydiphenyl)methane. $C_{13}H_{12}O$; mol wt 184.23. C 84.75%, H 6.57%, O 8.68%. Prepd from phenol and benzyl chloride in the presence of zinc chloride: Ziegenbein *et al.*, *Ber.* 88, 1906 (1955).

Crystals, mp 84°. bp 322°; bp_4 154-157°. Slightly sol in cold water; moderately sol in hot water; sol in organic solvents, glacial acetic acid, alkali hydroxide solns.

USE: Germicide, antiseptic; preservative; also in organic syntheses.

1144. Benzyl Salicylate. [118-58-1] 2-Hydroxybenzoic acid phenylmethyl ester; salicylic acid benzyl ester. $C_{14}H_{12}O_3$; mol wt 228.24. C 73.67%, H 5.30%, O 21.03%. Prepd from sodium salicylate and benzyl chloride: Volwiler, Vliet, *J. Am. Chem. Soc.* 43, 1672 (1921).



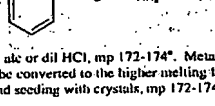
Thick liquid, slight, pleasant odor. d^{20} 1.175. bp_{25} 208°. Slightly sol in water; miscible with alcohol or ether.

USE: As fixer in perfumery; in sunscreen preparations.

1145. Benzyl Sulfide. [538-74-9] 1,1'-[Thiobis(methylene)]bisbenzene; dibenzylsulfide. $C_{14}H_{14}S$; mol wt 214.33. C 78.45%, H 6.58%, S 14.96%. $(C_6H_5CH_2)_2S$. Prepn: Runge *et al.*, *J. Prakt. Chem.* 11, 284 (1960). Manuf from benzyl chloride and Na_2S: Stucker, Brennan, US 2755305 (1956 to Pure Oil Co.).

Plates, mp 49°. Practically insol in water. Sol in alc, ether.

1146. *S*-Benzylthiuronium Chloride. [538-28-3] Carbamimidothioic acid phenylmethyl ester monohydrochloride. $C_8H_{11}ClN_2S$; mol wt 202.70. C 47.40%, H 5.47%, Cl 17.49%, N 13.82%, S 15.82%. Prepd by refluxing a mixture of 126 g benzyl chloride, 76 g thiourea, and 200 ml alcohol for 0.5 hr: Donleavy, *J. Am. Chem. Soc.* 58, 1004 (1936).



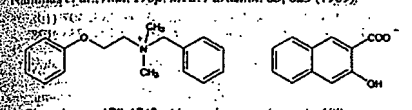
Crystals from alc or dil HCl, mp 172-174°. Metastable form, mp 146-148°. Can be converted to the higher melting form by dissolving in alcohol and seeding with crystals, mp 172-174°.

USE: Reagent for cobalt and nickel; identification and separation of carboxylic, sulfinic, and sulfonic acid.

1147. Benzylurea. [538-32-9] (Phenylmethyl)urea; benzylcarbamide. $C_8H_{10}N_2O$; mol wt 150.18. C 63.98%, H 6.71%, N 18.65%, O 10.65%. $C_6H_5CH_2NHCONH_2$. Prepn: Neville, McGee, *Can. J. Chem.* 41, 2123 (1963).

Crystals, mp 147-148°; dec in 200°. One gram dissolves in 60 ml warm water, 33 ml acetone; slightly sol in benzene, ether.

1148. Bephenium Hydroxynaphthoate. [3818-50-6] *N,N*-Dimethyl-*N*-(2-phenoxyethyl)benzenemethanaminium salt with 3-hydroxy-2-naphthalene carboxylic acid (1:1); bephenium embonate; Lecibis. $C_{38}H_{39}NO_4$; mol wt 443.53. C 75.82%, H 6.59%, N 3.16%, O 14.43%. Prepn: F. C. Copp, US 2918401 (1959 to Burroughs Wellcome). Mode of action: G. C. Cotes *et al.*, *Experientia* 30, 1265 (1974). Spectrophotometric determn: C. S. P. Sastry, M. Aruna, *Pharmazie* 43, 361 (1988). Efficacy against strongylosis in elephants: K. Chandrasekharan *et al.*, *Kerala J. Vet. Sci.* 13, 15 (1982). Clinical trial in hookworm infections: J. Nahonius *et al.*, *Ann. Trop. Med. Parasitol.* 83, 625 (1989).

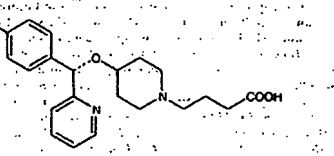


Crystals, mp 170-171°. Absorption max (water): 600 nm.

THERAP CAT: Anthelmintic (Nematodes).

THERAP CAT (VET): Anthelmintic (Nematodes).

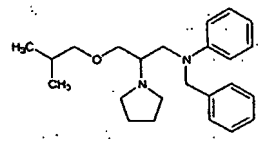
1149. Bepotastine. [190786-43-7] 4-[(*S*)-(4-Chlorophenyl)-2-pyridinylmethoxy]-1-piperidinebutanoic acid; betotastine. $C_{21}H_{25}ClN_2O_3$; mol wt 388.89. C 64.86%, H 6.48%, Cl 9.12%, N 7.20%, O 12.34%. Histamine H_1-receptor antagonist. Prepn (stereochem. unspec.): A. Koda *et al.*, EP 335586; *eidem*, US 4929618 (1989, 1990 both to Ube). Prepn of optically active salts: J. Kita *et al.*, EP 949260 (1999 to Ube; Tanabe Seiyaku). Pharmacology: M. Kato *et al.*, *Arzneim.-Forsch.* 47, 1116 (1997). Suppression of IL-5 production: O. Kaminuma *et al.*, *Biol. Pharm. Bull.* 21, 411 (1998). Antiallergic activity in animal models: M. Ueno *et al.*, *Pharmacology* 57, 206 (1998).



benzenesulfonate salt. [190786-44-8] Bepotastine besilate; TAU-284; Talion. $C_{21}H_{25}ClN_2O_3{\cdot}C_6H_6O_3S$; mol wt 547.06. Pale-grey prisms from acetonitrile, mp 161-163°. $[\alpha]_D^{20}$ +6.0° (c = 5 in methanol).

THERAP CAT: Antihistaminic.

1150. Bepridil. [64706-54-3] β-[(2-Methylpropoxy)methyl]-*N*-phenyl-*N*-(phenylmethyl)-1-pyrrolidineethanamine; 1-[2-(*N*-benzylanilino)-1-(isobutoxymethyl)ethyl]pyrrolidine; 1-isobutoxy-2-pyrrolidino-3-*N*-benzylanilinopropane; 3-isobutoxy-2-pyrrolidino-*N*-phenyl-*N*-benzylpropylamine. $C_{24}H_{34}N_2O$; mol wt 366.54. C 78.64%, H 9.35%, N 7.64%, O 4.36%. Calcium channel blocker with antianginal and antiarrhythmic properties. Prepn: R. F. Mauvernay *et al.*, DE 2310918; *eidem*, US 3962238; reissued with structure correction: N. Busch *et al.*, US RE 30577 (1973, 1976, 1981 all to CERM). *See* also: R. Y. Mauvernay *et al.*, DE 2802864 (1978 to CERM); *C.A.* 89, 179852s (1978). Cardiovascular pharmacology in dogs: M.-T. Michelin *et al.*, *Therapie* 32, 485 (1977). Mechanism of action studies: S. Vogel *et al.*, *J. Pharmacol. Exp. Ther.* 210, 378 (1979); C. Labrid *et al.*, *ibid.* 211, 546 (1979). Clinical comparison of hemodynamic and coronary changes: J.-P. Merillon *et al.*, *Therapie* 36, 123 (1981). Clinical evaluation in angina: M. K. Sharma *et al.*, *Am. J. Cardiol.* 61, 1210 (1988).



Viscous liquid, $bp_{0.1}$ 184°, $bp_{0.3}$ 192°. α_D^{20} 1.5538.

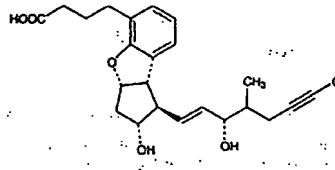
Hydrochloride monohydrate. [74764-40-2] CERM-1978; Cordium; Vascor; Unicordium. $C_{24}H_{34}N_2O{\cdot}HCl{\cdot}H_2O$; mol wt 421.02. Crystals, mp 91 ±2°. LD_{50} in mice (mg/kg): 1955 orally, 23.5 i.v. (Mauvernay, 1978).

THERAP CAT: Antianginal.

1151. Beractant. [108778-82-1] Surfactant TA; A-60386X; Surfacten; Survanta. Organic solvent extract of bovine lung, consisting mostly of phospholipids, modified by the addition of colfosceril palmitate, palmitic acid and tripalmitin. Prepn: JP 83 45299; Y. Tanaka *et al.*, US 4397839 (both 1983 to Tokyo Tanabe). Effect of protein component on surface activity: S. B. Hall *et al.*, *Am. Rev. Respir. Dis.* 145, 24 (1992). Pharmacology: J. J. Cummings *et al.*, *ibid.* 999. Metabolism in rabbits: J. F. Lewis *et al.*, *ibid.* 19. Evaluation of establishment of normal surfactant function in comparison with Exosurf: E. M. Scarpelli *et al.*, *Am. J. Perinatol.* 9, 414 (1992). Clinical trial in neonatal respiratory distress syndrome: M. D. Reller *et al.*, *Am. J. Dis. Child.* 145, 1017 (1991); E. M. Zola *et al.*, *Pediatrics* 91, 546 (1993).

THERAP CAT: Pulmonary surfactant.

1152. Beraprost. [88430-50-6] 2,3,3a,8b-Tetrahydro-2-hydroxy-1-(3-hydroxy-4-methyl-1-octen-6-ynyl)-1*H*-cyclopenta(*b*)-benzofuran-5-butanoic acid; *dl*-16-methyl-18,19-tetradehydro-5,6,7-trinor-4,8-inter-*m*-phenylene prostaglandin I_1; *dl*-4-[(1*R*,2*R*,-3a*S*,8b*S*)-1,2,3a,8b-tetrahydro-2-hydroxy-[(3*S*,4*RS*)-3-hydroxy-4-methyl-oct-6-yne-(*E*)-1-enyl]-5-cyclopenta(*b*)benzofuranyl]butanoic acid; beraprost; ML-1229. $C_{24}H_{30}O_5$; mol wt 398.49. C 72.34%, H 7.59%, O 20.08%. Platelet aggregation inhibitor; stable analog of prostacyclin, *q.v.* Prepn: K. Ohno *et al.*, EP 84856; *eidem*, US 4474802 (1983, 1984 both to Toray); *eidem*, *Adv. Prostaglandin Thromboxane Leukotriene Res.* 15, 279 (1985). PGI_2 receptor binding: N. Kajikawa *et al.*, *Arzneim.-Forsch.* 39, 495 (1989). Series of articles on pharmacology: *ibid.* 856-876. Clinical pharmacokinetics: J.-L. Demolis *et al.*, *J. Cardiovasc. Pharmacol.* 22, 711 (1993). Clinical trial in intermittent claudication: M. Lievre *et al.*, *ibid.* 27, 788 (1996); in diabetic angiopathy: Y. Okuda *et al.*, *Prostaglandins* 52, 375 (1996).

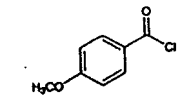


Sodium salt. [88475-69-8] ML-1129; TRK-100; Domer; Procylin. $C_{24}H_{29}NaO_5$; mol wt 420.47.

THERAP CAT: Antithrombotic; vasodilator (peripheral).

1153. Berbamine. [478-61-5] (4a*S*,16a*R*)-3,4,4a,5,16a,17,-18,19-Octahydro-21,22,26-trimethoxy-4,17-dimethyl-16*H*-1,24:6,9-dietheno-11,15-metheno-2*H*-pyrido[2',3':17,18][1,-11]dioxacyclooicosino[2,3,4-*ij*]isoquinolin-12-ol; 6,6',7-trimethoxy-2,2'-dimethylberbaman-12-ol; berbenine. $C_{37}H_{40}N_2O_6$; mol wt 608.72. C 73.00%, H 6.62%, N 4.60%, O 15.77%. Alkaloid found in various members of Berberis family. Used as a traditional medicine in China as antipyretic, antidiarrhoea and as a tonic. Identification in *Berberis vulgaris*: C. Rüdel, *Arch. Pharm.* 229, 631 (1895); isoln from *Atherosperma moschatum* Labill., *Monimiaceae*: I. R. C. Bick *et al.*, *Aust. J. Chem.* 9, 111 (1956). Structure: F. von Bruchhausen *et al.*, *Ann.* 507, 144 (1933); configuration: Y.

673. *p*-Anisoyl Chloride. [100-07-2] 4-Methoxybenzoyl chloride. $C_8H_7ClO_2$; mol wt 170.59. C 56.33%, H 4.14%, Cl 20.78%, O 18.76%. Prepd from *p*-anisic acid and thionyl chloride: Vanderhaeghe *et al., J. Pharm. Pharmacol.* 6, 119 (1954).



Crystals or liquid. mp 22°. bp ~262-263° with slight decompn. Dec by water or alcohol. Sol in acetone, benzene.

Caution: Vapors can cause serious eye burns. Sealed containers may explode, because slow decompn at room temp may build up pressure. *Ref:* Carroll, *Chem. Eng. News* 38, 40 (Aug. 22, 1960).

674. Anistreplase. [81669-57-0] Anisoylated plasminogen streptokinase activator complex; APSAC; BRL-26921; Eminase; Multilase. Binary complex of streptokinase and human plasminogen in which the catalytic site is reversibly blocked by a *p*-methoxybenzoyl group without affecting the fibrin-binding site. Prepn and fibrinolytic activity: R. A. G. Smith, J. G. Winchester, EP 28489; *eidem*, US 4808405 (1981, 1989 both to Beecham). Deacylation of the fibrin-bound complex initiates thrombolysis: R. A. G. Smith *et al., Nature* 290, 505 (1981); D. Matsuo *et al., Thromb. Res.* 24, 347 (1981). Effect on hemostasis in humans: D. H. Staniforth *et al., Eur. J. Clin. Pharmacol.* 24, 751 (1983). Pharmacokinetics: M. Been *et al., Int. J. Cardiol.* 11, 53 (1986). Evaluation of thrombolytic efficacy in myocardial infarction: W. Kasper *et al., Am. J. Cardiol.* 58, 418 (1986); in major pulmonary embolism: J. H. Brett *et al., Aust. N.Z. J. Med.* 17, 77 (1987). Controlled clinical trial in acute myocardial infarction: S. Ikram *et al., Br. Med. J.* 293, 786 (1986). Review of mechanism of action, pharmacology and therapeutic use: J. P. Monk, R. C. Heel, *Drugs* 34, 25-49 (1987).

THERAP CAT: Thrombolytic.

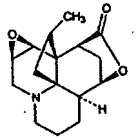
675. Annatto. [1393-63-1] C.I. Natural Orange 4; C.I. 75120; arnotta; annotta. Coloring matter from seeds of *Bixa orellana* L., *Bixaceae*. Extraction from seed: Barnett, Espoy, US 2815287 (1957); Kocher, US 2831775 (1958). Contains bixins, *q.v.*, and several other yellow to orange-red pigments which give carotene reactions: Diemair *et al., Naturwissenschaften* 39, 211 (1933). Review of chemistry and applications: P. Collins, *Food Ingred. Proc. Int.* 13, 23-27 (1992). *See also: Colour Index* vol. 3 (3rd ed., 1971) p. 3233.

Sol in alcohol, ether, oils.

USE: Food coloring in dairy products, esp butter and cheese, flour confectionary, fish, meat products, soft drinks, snack foods and dry mixes. In wood stains, polish, and varnishes. Spice or condiment. Insect repellent.

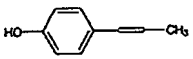
676. Annexins. Family of calcium and phospholipid binding proteins; virtually ubiquitous in both animal and plant cells. Characterized by a common structure composed of 4 or 8 homologous repeats of ~70 amino acids. Involved in membrane trafficking, transmembrane channel activity, inhibition of phospholipase A2, and inhibition of coagulation. Known variously by such names as *synexin*, *lipocortin*, *anchorin*, and *calpactin*, the term annexins was chosen for their ability to bind, or "annex", to cellular membranes. Description of nomenclature: M. J. Crumpton, J. R. Dedman, *Nature* 345, 212 (1990). Isoln of synexin from bovine adrenal medullary tissue: C. E. Creutz *et al., J. Biol. Chem.* 253, 2858 (1978). Review of discovery, molecular biology and bioactivites: P. Raynal, H. B. Pollard, *Biochim. Biophys. Acta* 1197, 63-93 (1994); of annexins in plant cells: G. B. Clark, S. J. Roux, *Plant Physiol.* 109, 1133-1139 (1995). Review of three-dimensional structure: S. Liemann, R. Huber, *Cell. Mol. Life Sci.* 53, 516-521 (1997). Review of role in plasminogen binding: H.-M. Kaug et al., *Trends Cardiovasc. Med.* 9, 92-102 (1999); K. A. Hajjar, S. Krishnan, *ibid.* 128-138; of role in membrane fusion: H. Kubista *et al., Subcell. Biochem.* 34, 73-131 (2000); as nucleotide binding proteins: J. Bandorowicz-Pikula *et al., BioEssays* 23, 170-178 (2001). Comprehensive description: V. Gerke, S. E. Moss, *Physiol. Rev.* 82, 331-371 (2002).

677. Annotiuine. [559-49-9] $C_{16}H_{21}NO_3$; mol wt 275.34. C 69.79%, H 7.69%, N 5.09%, O 17.43%. Isoln from *Lycopodium annotinum* L., *Lycopodiaceae:* Manske, Marion, *Can. J. Res.* 21B, 92 (1943). Structure: Przybylska, Marion, *Can. J. Chem.* 35, 1075 (1957); Wiesner *et al., Tetrahedron* 4, 87 (1958); Przybylska, Ahmed, *Acta Crystallogr.* 11, 718 (1958). Stereochemistry: Wiesner *et al., Tetrahedron Lett.* 1961, 187; Ho, *ibid.* 1969, 1307. Synthesis: Wiesner *et al., Can. J. Chem.* 47, 433 (1969). Biogenesis: Leete, *Tetrahedron* 3, 313 (1958).



Brilliant prisms from chloroform + methanol, mp 232°. Sol in chloroform, dil HCl. Sparingly sol in methanol.

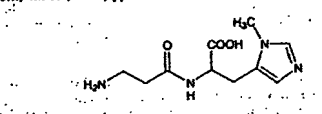
678. *p*-Anol. [539-12-8] 4-(1-Propenyl)phenol; *p*-propenylphenol; 4-hydroxy-1-propenylbenzene. $C_9H_{10}O$; mol wt 134.18. C 80.56%, H 7.51%, O 11.92%. Prepn from anethole: Stoermer, Kahlert, *Ber.* 34, 1812 (1901); from 4-propenylphenylmagnesium bromide: Quelet, *Bull. Chim. Soc.* [4] 45, 268 (1929).



Leaflets from boiling water. Weak odor of cloves, resembling that of eugenol. Spicy, pungent taste. mp 93-94°. bp_{760} 250° (dec); bp_{14} 138-140°. Slightly sol in hot water. Freely sol in dimethylformamide, other organic solvents. Sol in aq solns of KOH and NaOH.

USE: Intermediate in the synthesis of estrogens.

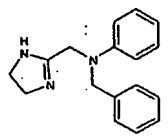
679. Anserine. [584-85-0] *N*-β-Alanyl-3-methyl-L-histidine; α-(β-aminopropionylamino)-β-(1-methyl-5-imidazolyl)-propionic acid; 3-methyl-*N*-α-(β-alanyl)-L-histidine. $C_{10}H_{16}N_4O_3$; mol wt 240.26. C 49.99%, H 6.71%, N 23.32%, O 19.98%. First found in muscles of geese, later in many more animals, but not in man, cow, horse, or dog. Isoln: Ackermann, *Z. Physiol. Chem.* 183, 1 (1929); Wolff, Wilson, *J. Biol. Chem.* 109, 565 (1935). Synthesis: Behrens, du Vigneaud, *J. Biol. Chem.* 120, 517 (1937); Rinderknecht *et al., J. Org. Chem.* 29, 1968 (1964). *Review:* M. Guggenheim, *Die biogenen Amine* (Karger, Basel & New York, 4th ed., 1951) pp 439-446, 502.



L-Form. Needles from dil alc, dec 240-242°. $[\alpha]_D^{20}$ +12.3° (c = 5). pK_1 2.64; pK_2 7.04; pK_3 9.49. The dried material is very hygroscopic. Freely soluble in water. Slightly sol in methanol, even less in ethanol.

Nitrate. $C_{10}H_{16}N_4O_3 \cdot HNO_3$. Needles from dil methanol, mp 226-228°.

680. Antazoline. [91-75-8] 4,5-Dihydro-*N*-phenyl-*N*-(phenylmethyl)-1*H*-imidazole-2-methanamine; 2-(*N*-benzylanilinomethyl)-2-imidazoline; phenazoline; 2-(*N*-phenyl-*N*-benzylaminomethyl)imidazoline; imidamine; 5512-M. $C_{17}H_{19}N_3$; mol wt 265.35. C 76.95%, H 7.22%, N 15.84%. Prepn: Mieszcher, Klarer, US 2449241 (1948 to Ciba). HPLC determn in ophthalmic solutions: S. C. Ruckmick *et al., J. Pharm. Sci.* 84, 502 (1995). Clinical trial in combination with naphazoline in allergic conjunctivitis: M. B. Abelson *et al., Arch. Ophthalmol.* 108, 520 (1990).



Crystals, mp 120-122°.

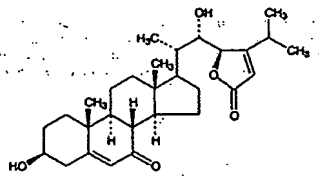
Hydrochloride. [2508-72-7] Antistine; Antasten. $C_{17}H_{19}N_3 \cdot HCl$; mol wt 301.81. Bitter crystals producing temporary numbness of the tongue. mp 237-241°. uv max: 242 nm ($E_{1cm}^{1\%}$ 495 to 515); min 222 nm. One gram dissolves in 40 ml water, in 25 ml alc. Practically insol in ether, benzene, chloroform. pH (1% aq soln): 6.3.

Phosphate. [154-68-7] $C_{17}H_{19}N_3 \cdot H_3PO_4$. Crystals. Bitter taste. mp 194-198°. Sol in water. Sparingly sol in methanol. Practically insol in benzene, ether. pH (2% aq soln): 4.5.

THERAP CAT: Antihistaminic.

THERAP CAT (VET): Antihistaminic.

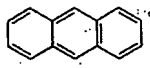
681. Antheridiol. [22263-79-2] (3β,22*S*,23*R*)-3,22,23-Trihydroxy-7-oxostigmasta-5,24(28)-dien-29-oic acid γ-lactone; 3β,22,23-trihydroxy-24-(carboxymethylene)cholest-5-en-7-one 23,24-lactone. $C_{29}H_{42}O_5$; mol wt 470.64. C 74.01%, H 8.99%, O 17.00%. The first specific functioning sex hormone to be identified in the plant kingdom. A diffusible substance secreted by the female mycelium of the filamentous water molds *Achlya bisexualis* and *A. ambisexualis*, which induces the growth of antheridial hyphae in the male plant, thereby initiating sexual reproduction in the species. Isoln and preliminary chemical data: Raper, Haagen-Smit, *J. Biol. Chem.* 143, 311 (1942). Isoln of crystalline material: McMorris, Barksdale, *Nature* 215, 320 (1967). Structure: Arsenault *et al., J. Am. Chem. Soc.* 90, 5635 (1968). Synthesis: J. A. Edwards *et al., ibid.* 91, 1248 (1969); J. H. Fried, J. A. Edwards, US 3547911 (1970 to Syntex). Stereochemical proposal: Green *et al., Tetrahedron* 27, 1999 (1971). Absolute stereochemistry and alternate syntheses: Edwards *et al., Tetrahedron Lett.* 1972, 791; T. C. McMorris *et al., ibid.* 2673; *eidem, J. Org. Chem.* 39, 669 (1974). *Reviews:* Barksdale, *Ann. N.Y. Acad. Sci.* 144, 313-319 (1967); *idem, Science* 166, 831-837 (1969); T. C. McMorris, *Lipids* 13, 716-722 (1978).



Colorless crystals from methanol, mp 250-255°. uv max (ethanol): 220 nm (ε 17,000). Sol in hot methanol. Slightly sol in chloroform; very slightly sol in water.

USE: Control and regulation of plant fertility.

682. Anthracene. [120-12-7] $C_{14}H_{10}$; mol wt 178.23. C 94.34%, H 5.66%. Obtained from coal tar, *q.v.*: Dumas, Laurent, *Ann.* 5, 10 (1833); Laurent, *Ann.* 34, 287 (1840); Anderson, *Ann.* 122, 294 (1862); *J. Chem. Soc.* 15, 44 (1862); Auerbach, *Das Anthracen und seine Derivate* (Braunschweig, 1880); Perkin, *J. Soc. Arts* 27, 572 (1879); Lunge, *Coal Tar and Ammonia* (1916); Barnett, *Anthracene and Anthraquinone* (London, 1921); Nanson, *Text. Color.* 48, 605, 678, 751 (1926); 49, 19, 246, 557, 593 (1927); Houben, Fischer, *Das Anthracen und die Anthrachinone* (Leipzig, 1929); Bormann, *Der Teer* (Leipzig, 1940); Schumann, *Kokereiteer* (Stuttgart, 1940). Extensive patent literature on purification. Prepn of very pure anthracene from synthetic anthraquinone: Clar, *Ber.* 72, 1645 (1939). *Review:* E. Clar, *Polycyclic Hydrocarbons* Vol. 1 & 2 (Academic Press, New York, 1964). Review of toxicology and human exposure: *Toxicological Profile for Polycyclic Aromatic Hydrocarbons* (PB95-264370, 1995) 487 pp.



Monoclinic plates from alc. Sublimes. When pure, colorless with violet fluorescence; when impure (due to tetracene, naphthacene), yellow with green fluorescence. Strongly triboluminescent and triboelectric. d_4^{27} 1.25. mp 218°. bp_{760} 342°. Absorption spectrum: Clar, *Ber.* 65, 506 (1932). Less soluble than the isomeric phenanthrene. Insol in water; one gram dissolves in 67 ml abs alcohol, 70 ml methanol, 62 ml benzene, 85 ml chloroform, 200 ml ether, 31 ml carbon disulfide, 86 ml carbon tetrachloride, 125 ml toluene. Anthracene darkens in sunlight. According to Downs, US 1303639 (1919), when solns of crude anthracene in coal tar naphtha are exposed to ultraviolet irradiation, the anthracene is precipitated as dianthracene (*para*-anthracene) which is reconverted to anthracene by sublimation. Forms molecular addn products with nitro compounds.

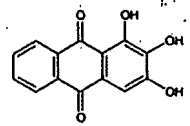
Picric acid complex. mp 139°.

sym-Trinitrobenzene complex. mp 164°.

Trinitrotoluene complex. mp 162°.

USE: Important source of dyestuffs (manuf anthraquinone, alizarin dyes).

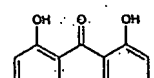
683. Anthragallol. [602-64-2] 1,2,3-Trihydroxy-9,10-anthracenedione; 1,2,3-trihydroxyanthraquinone; anthragallic acid; anthracene brown. $C_{14}H_8O_5$; mol wt 256.21. C 65.63%, H 3.15%, O 31.22%. From gallic acid and benzoic acid with sulfuric acid at 125° or from phthalic anhydride and pyrogallol with sulfuric acid at 160°: Seuberlich, *Ber.* 10, 39 (1877). Other methods: Kubota, Perkin, *J. Chem. Soc.* 127, 1889 (1925); Perkin, Story, *ibid.* 1929, 1399; Cross, Perkin, *ibid.* 1930, 292. Absorption spectrum: Meyer, Fischer, *Ber.* 46, 85 (1913).



Brown crystals, mp 312-313°. Sublimes 290°. Slightly sol in water, chloroform; sol in alcohol, ether, glacial acetic acid. Its soln in concd H_2SO_4 is reddish-brown. Greenish-brown soln in ammonia water changes to blue on heating. Forms salts with Na, K, Ba, Tl, Pb, La, Co, Nd, Co.

Trimethyl ether. $C_{17}H_{14}O_5$. Yellow needles from benzene + petr ether, mp 168°. Insol in water solns of alkalies.

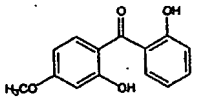
684. Anthralin. [1143-38-0] 1,8-Dihydroxy-9(10*H*)-anthracenone; 1,8-dihydroxyanthrone; dithranol; Anthraforte; Anthranol; Anthrascalp; Antraderm; Cignolin; Dithrocream; Drithocreme; Dritho-Scalp; Micanol; Psoradrate; Psoriderm. $C_{14}H_{10}O_3$; mol wt 226.23. C 74.33%, H 4.46%, O 21.22%. Prepn: Y. Hirosé, *Ber.* 45, 2474 (1912); K. Zahn, H. Koch, *ibid.* 71B, 172 (1938). Revised structure: H. M. Avdovich, G. A. Neville, *Can. J. Spectrosc.* 25, 110 (1980); F. R. Ahmed, *Acta Crystallogr.* B36, 3184 (1980). Historical review: R. E. Ashton *et al., J. Am. Acad. Dermatol.* 9, 173-192 (1983). Review of mechanism of action: L. Kemény *et al., Skin Pharmacol.* 3, 1-20 (1990); of clinical pharmacology and efficacy in psoriasis: G. Mahrle, *Clin. Dermatol.* 15, 723-737 (1997).



Lemon yellow leaflets or needles from ligroin, mp 176-181°. Practically insol in water. Sol in chloroform, acetone, benzene. Slightly sol in alcohol, ether, glacial acetic acid. Sol in dil NaOH with yellow color and green fluorescence, becoming orange-red on exposure to air.

THERAP CAT: Antipsoriatic.

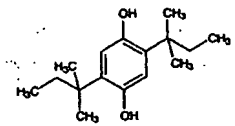
3303. Dioxybenzone. [131-53-3] (2-Hydroxy-4-methoxyphenyl)(2-hydroxyphenyl)methanone; 2,2'-dihydroxy-4-methoxybenzophenone; 4-methoxy-2,2'-dihydroxybenzophenone; benzophenone-8; Cyasorb UV 24 (obsolete); Spectra-Sorb UV 24. $C_{14}H_{12}O_4$; mol wt 244.24. C 68.85%, H 4.95%, O 26.20%. Prepn: Hardy *et al.*, US 2853521 (1958 to Am. Cyanamid).



Yellow powder, mp 68°. Soly in g/100 ml at 25°: ethanol 21.8; isopropanol 17; propylene glycol 6.2; ethylene glycol 3.0; *n*-hexane 1.5.

THERAP CAT: Ultraviolet screen.

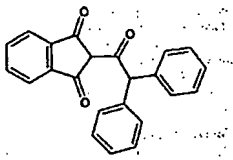
3304. 2,5-Di-*tert*-pentylhydroquinone. [79-74-3] 2,5-Bis(1,1-dimethylpropyl)-1,4-benzenediol; 2,5-di-*tert*-amylhydroquinone; 2,5-bis(1,1-dimethylpropyl)hydroquinone; Santovar A. $C_{16}H_{26}O_2$; mol wt 250.38. C 76.75%, H 10.47%, O 12.78%. Prepn: Erickson, GB 596461 (1948 to Mathieson Alkali Works).



Crystals, mp 179.4-180.4°.

USE: As a staining protector in rubber.

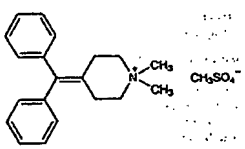
3305. Diphacinone. [82-66-6] 2-(Diphenylacetyl)-1*H*-indene-1,3(2*H*)-dione; 2-diphenylacetyl-1,3-diketohydrindene; 2-diphenylacetyl-1,3-indandione; diphenadione; U-1363; Diphacin; Ditrac; Ramik. $C_{23}H_{16}O_3$; mol wt 340.37. C 81.16%, H 4.74%, O 14.10%. Anticoagulant; inhibits vitamin K-dependent synthesis of factors II, VII and X. Prepn: D. G. Thomas, US 2672483 (1954 to Upjohn). Anticoagulant effects in rodents: J. T. Correll *et al.*, *Proc. Soc. Exp. Biol. Med.* 80, 139 (1952). Metabolism in rats and mice: C. C. Yu *et al.*, *Drug Metab. Dispos.* 10, 645 (1982). LC/MS determn in commercial rodenticides: M. Z. Mesner, R. A. Flurer, *J. Chromatogr. A* 891, 249 (2000).



Pale yellow crystals from ethanol, mp 146-147°. Practically insol in water. Slightly sol in benzene, hot ethanol. Sol in acetone, acetic acid. LD_{50} orally (mg/kg): 3 in rats; 340 in mice; 35 in rabbits (Correll).

USE: Rodenticide.

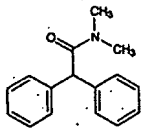
3306. Diphemanil Methylsulfate. [62-97-5] 4-(Diphenylmethylene)-1,1-dimethylpiperidinium methyl sulfate; *p*-(α-phenylbenzylidene)-1,1-dimethylpiperidinium methylsulfate; *N,N*-dimethyl-4-piperidylidene-1,1-diphenylmethane methylsulfate; Prantal. $C_{21}H_{27}NO_4S$; mol wt 389.51. C 64.75%, H 6.99%, N 3.60%, O 16.43%, S 8.23%. Anticholinergic. Prepn: N. Sperber *et al.*, *J. Am. Chem. Soc.* 73, 5010 (1951); N. Sperber *et al.*, US 2739968 (1956 to Schering). Pharmacological properties and toxicity data: S. Margolin *et al.*, *Proc. Soc. Exp. Biol. Med.* 78, 576 (1951). Clinical evaluation in treatment of gustatory sweating: O. Laccourreye *et al.*, *Laryngoscope* 100, 1651 (1990). Clinical pharmacokinetics: A. M. Vidal *et al.*, *Eur. J. Clin. Pharmacol.* 42, 689 (1992).



Crystals, mp 194-195°. Soluble in water. LD_{50} in rats, mice, guinea pigs (mg/kg): 1107, 64, 404 orally (Margolin).

THERAP CAT: In treatment of hyperhidrosis.

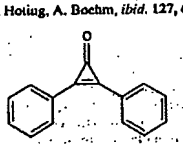
3307. Diphenamid. [957-51-7] *N,N*-Dimethyl-α-phenylbenzeneacetamide; *N,N*-dimethyl-2,2-diphenylacetamide; *N,N*-dimethyl-α,α-diphenyl acetamide; 2,2-diphenyl-*N,N*-dimethylacetamide; L-34314; Dymid; Enide. $C_{16}H_{17}NO$; mol wt 239.31. C 80.30%, H 7.16%, N 5.85%, O 6.69%. Selective pre-emergence herbicide. Prepn: Cheney *et al.*, *J. Org. Chem.* 17, 770 (1952). Toxicity study: G. W. Bailey, J. L. White, *Residue Rev.* 10, 97 (1965).



Crystals from ethyl acetate, mp 134.5-135.5°. Soluble in water, acetone, dimethylformamide, xylene, phenyl Cellosolve. LD_{50} orally in rats: 700 mg/kg (Bailey, White).

USE: Herbicide.

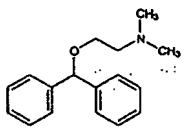
3308. Diphencyprone. [886-38-4] 2,3-Diphenyl-2-cyclopropen-1-one; 1,2-diphenylcyclopropenone; DPC. $C_{15}H_{10}O$; mol wt 206.24. C 87.35%, H 4.89%, O 7.76%. Contact allergen, possibly the smallest neutral aromatic specie. Prepn: R. Breslow *et al.*, *J. Am. Chem. Soc.* 81, 247 (1959). Crystal structure: H. L. Ammon, *ibid.* 95, 7093 (1973). Strain energy: A. Greenberg *et al.*, *ibid.* 105, 6855 (1983). Mechanism of photodissociation: Y. Hirata, N. Mataga, *Chem. Phys. Lett.* 193, 287 (1992). Report as contact sensitizer: B. M. Hausen, J. State, *Chem. Ind.* 1980, 699. Clinical evaluation in alopecia totalis: B. Monk, *Clin. Exp. Dermatol.* 14, 154 (1989); of children with alopecia areata: S. MacDonald Hull *et al.*, *Br. J. Dermatol.* 125, 164 (1991). Review of clinical efficacy: E. Hoting, A. Boehm, *ibid.* 127, 625-629 (1992).



Crystallizes as monohydrate from cyclohexane, mp 87-90°. d 1.202 g/cm³. uv max (CH_3CN): 297, 282, 226, 220 nm (log ε 4.3, 4.25, 4.13, 4.16). mp (anhydrous): 118-120°.

THERAP CAT: Antialopecia agent.

3309. Diphenhydramine. [58-73-1] 2-Diphenylmethoxy-*N,N*-dimethylethanamine; 2-(benzhydryloxy)-*N,N*-dimethylethylamine; β-dimethylaminoethyl benzhydryl ether; *O*-benzhydryldimethylaminoethanol; β-dimethylaminoethanol diphenylmethyl ether; α-(2-dimethyluminoethoxy)diphenylmethane; benzhydramine. $C_{17}H_{21}NO$; mol wt 255.35. C 79.96%, H 8.29%, N 5.49%, O 6.27%. Prepn: G. Rieveschl, Jr., US 2421714 (1947 to Parke, Davis); *see also* H. Martin *et al.*, US 2397799 (1946 to Geigy). Toxicology study: O. M. Gruhzit, R. A. Fisken, *J. Pharmacol. Exp. Ther.* 89, 227 (1947). Comprehensive description of the hydrochloride: I. J. Holcomb, S. A. Fusari, *Anal. Profiles Drug Subs.* 3, 173-232 (1974). Clinical pharmacokinetics: J. M. Scavone *et al.*, *J. Clin. Pharmacol.* 38, 603 (1998). Clinical trial in insomnia: K. Rickels *et al.*, *ibid.* 23, 235 (1983).



$bp_{0.8}$ 150-165°.

Hydrochloride. [147-24-0] Allergina; Benadryl; Benocten; Dibondrin; Dolestan; Hafbmond; Noctomin; Nytol; Sedopretten; Sekundal-D; Sominex; Unisom Sleepgels. $C_{17}H_{21}NO.HCl$; mol wt 291.82. Crystals from abs alcohol + ether, mp 166-170°. Bitter taste. Slowly darkens on exposure to light. Stable under ordinary conditions. One gram dissolves in 1 ml water, 2 ml alcohol, 2 ml chloroform, 50 ml acetone. Very slightly sol in benzene, ether. pH of 1% aq soln about 5.5. The aq soln forms a pink precipitate with acid Reinecke's salt soln. LD_{50} orally in rats: 500 mg/kg (Gruhzit, Fisken).

THERAP CAT: Antihistaminic; sedative, hypnotic.

THERAP CAT (VET): Antihistaminic. Also in motion sickness.

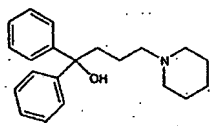
3310. Diphenic Acid. [482-05-3] [1,1'-Biphenyl)-2,2'-dicarboxylic acid; *o,o'*-bibenzoic acid. $C_{14}H_{10}O_4$; mol wt 242.23. C 69.42%, H 4.16%, O 26.42%. Prepd from diazotized anthranilic acid by treatment with a cuproammonia-sulfite reducing agent: Vorländer, Meyer, *Ann.* 320, 122 (1902); Atkinson, Lawler, *Org. Synth.* coll. vol. 1 (2nd ed, 1941) p 222. By chromic acid oxidation of phenanthrenequinone: Roberts, Johnson, *J. Am. Chem. Soc.* 47, 1399 (1925). By heating potassium *o*-bromobenzoate with copper powder: Hurtley, *J. Chem. Soc.* 1929, 1870.

Monoclinic prismatic rods upon slow cooling from water, leaflets from hot water, needles by careful sublimation. mp 228-229°. The acid aq soln is 0.0052*N* at 25°; soluble in the usual organic solvents.

Dimethyl ester. $C_{16}H_{14}O_4$. Monoclinic prismatic plates, tabs from methanol, mp 73.5°; bp_{14} 204-206°.

Diethyl ester. $C_{18}H_{18}O_4$. Cubes from alcoholic HCl, mp 42°.

3311. Diphenidol. [972-02-1] α,α-Diphenyl-1-piperidinebutanol; 1,1-diphenyl-4-piperidino-1-butanol; diphenyl-[3-(1-piperidyl)propyl]carbinol; defenidol; SKF-478. $C_{21}H_{27}NO$; mol wt 309.45. C 81.51%, H 8.79%, N 4.53%, O 5.17%. Prepn: Mietzsch, Marxer, US 2411664 (1946 to Ciba); Barrett, Wilkinson, GB 683950 (1952 to Wellcome Foundation), *C.A.* 48, 2112e (1954). Structure-activity studies: Gautier *et al.*, *Med. Pharmacol. Exp.* 13, 25 (1965). Clinical studies: Cutt *et al.*, *Aerosp. Med.* 39, 682 (1968); Benson, *ibid.* 40, 589 (1969). Acute toxicity: E. I. Goldenthal, *Toxicol. Appl. Pharmacol.* 18, 185 (1971).

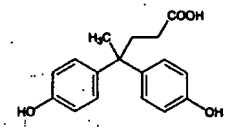


Needles from petr ether, mp 104-105°. LD_{50} s.c. in rats: 50 mg/kg (Goldenthal).

Hydrochloride. [3254-89-5] SKF-478-A; Ansmin; Cefudol; Celmidol; Difenidolin; Maniol; Mecalmin; Pineroro; Satanolon; Teesdol; Vontrol; Wansar. $C_{21}H_{27}NO.HCl$; mol wt 345.91. Crystals from chloroform + ethyl acetate, mp 212-214°. Freely sol in methanol; sol in water, chloroform. Practically insol in ether, benzene, petr ether.

THERAP CAT: Antiemetic.

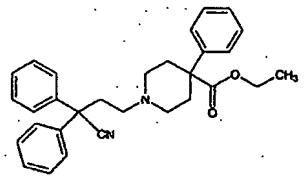
3312. Diphenolic Acid. [126-00-1] 4-Hydroxy-γ-(4-hydroxyphenyl)-γ-methylbenzenebutanoic acid; 4,4-bis[4'-hydroxyphenyl]pentanoic acid; γ,γ-bis-(*p*-hydroxyphenyl)valeric acid; DPA. $C_{17}H_{18}O_4$; mol wt 286.32. C 71.31%, H 6.34%, O 22.35%. Prepd by condensing 2.25-4.0 moles of phenol with one mole of levulinic acid in the presence of HCl: GB 768206 (1957 to S. C. Johnson & Son); from one mole of phenol, 0.5 mole levulinic acid and HCl, H_2SO_4 or H_3PO_4: Bader, Kantowicz, *J. Am. Chem. Soc.* 76, 4465 (1954); Bader, US 2933520 (1960 to S. C. Johnson & Son).



Crystals from hot water. Higher melting modification, mp 171-172°. Appreciably sol in hot water; sol in acetone, acetic acid, ethanol, isopropanol, methyl ethyl ketone.

USE: Intermediate for surface coatings, lubricating oil additives, cosmetics, surfactants, plasticizers, textile chemicals.

3313. Diphenoxylate. [915-30-0] 1-(3-Cyano-3,3-diphenylpropyl)-4-phenyl-4-piperidinecarboxylic acid ethyl ester; 1-(3-cyano-3,3-diphenylpropyl)-4-phenylisonipecotic acid ethyl ester; ethyl 1-(3-cyano-3,3-diphenylpropyl)-4-phenylisonipecotate; ethyl 1-(3-cyano-3,3-diphenylpropyl)-4-phenyl-4-piperidinecarboxylate; 2,2-diphenyl-4-(4-carbethoxy-4-phenylpiperidino)butyronitrile; R-1132. $C_{30}H_{32}N_2O_2$; mol wt 452.59. C 79.61%, H 7.13%, N 6.19%, O 7.07%. Prepn: Janssen, US 2898340 (1959). Pharmacokinetics and metabolism: Karim *et al.*, *J. Pharmacol. Exp. Ther.* 177, 546 (1971); *Clin. Pharmacol. Ther.* 13, 407 (1972). *See also* Difenoxin, the active metabolite of diphenoxylate. Comprehensive description: D. D. Hung, *Anal. Profiles Drug Subs.* 7, 149-169 (1978).



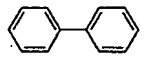
Hydrochloride. [3810-80-8] $C_{30}H_{32}N_2O_2.HCl$. Crystals, mp 220.5-222°. uv max (methanol): 252, 258, 264 nm. Soly in mg/ml at 25°: acetic acid 500; DMF 500; chloroform 360; methanol >50; ethanol 3; water 0.8; hexane 0.5.

Mixture of hydrochloride with atropine sulfate. Lomotil; Diarsed; Reasec.

Note: This is a controlled substance (opiate): 21 CFR, 1308.12.

THERAP CAT: Antiperistaltic; antidiarrheal.

3314. Diphenyl. [92-52-4] 1,1'-Biphenyl; bibenzene; phenylbenzene. $C_{12}H_{10}$; mol wt 154.21. C 93.46%, H 6.54%. Toxicity data: Deichmann *et al.*, *J. Ind. Hyg. Toxicol.* 29, 1 (1947). *Review:* W. C. Weaver *et al.*, in *Kirk-Othmer Encyclopedia of Chemical Technology* vol. 7 (Wiley-Interscience, New York, 3rd ed., 1979) pp 782-793.



Colorless leaflets; pleasant, peculiar odor. d 1.041. mp 69-71°. bp 254-255°. n_D^{77} 1.588. Insol in water. Sol in alc, ether. LD_{50} orally in rats: 3280 mg/kg (Deichmann).

Caution: Potential symptoms of overexposure are irritation of throat and eyes; headache, nausea, fatigue and numb limbs; liver